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L1             1 S WO2000038666/PN
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     19 NOV 2004
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L4           245 S E3-E5
L5            15 S L4 AND FBPASE
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L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:456867 CAPLUS
DOCUMENT NUMBER: 133:84284
TITLE: A combination of fructose-1,6-bisphosphatase (FBPase) inhibitors and insulin sensitizers for the treatment of diabetes
INVENTOR(S): Erion, Mark D.; Vanpoelje, Paul
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 306 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

same inventors

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038666	A2	20000706	WO 1999-US30713	19991222 <--
WO 2000038666	A3	20011129		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2354053	AA	20000706	CA 1999-2354053	19991222
EP 1143955	A2	20011017	EP 1999-964313	19991222
EP 1143955	A3	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9917005	A	20020402	BR 1999-17005	19991222
JP 2003515523	T2	20030507	JP 2000-590620	19991222
AU 771039	B2	20040311	AU 2000-20583	19991222
RU 2227749	C2	20040427	RU 2001-120726	19991222
ZA 2001005016	A	20020919	ZA 2001-5016	20010619
NO 2001003115	A	20010824	NO 2001-3115	20010621
PRIORITY APPLN. INFO.:			US 1998-114718P P	19981224
			WO 1999-US30713 W	19991222

OTHER SOURCE(S): MARPAT 133:84284

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               261367-07-1/BI OR 261367-08-2/BI)
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=> d ibib abs 1-6

L3 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:523110 CAPLUS
DOCUMENT NUMBER: 141:71536
TITLE: Preparation of 2-(5-phosphono)furanyl substituted heteroaromatic compounds as fructose-1,6-bisphosphatase (FBPase) inhibitors for use in combination with insulin sensitizers for the treatment of diabetes
INVENTOR(S): Erion, Mark D.; Van Poelje, Paul D.
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: U.S., 109 pp., Cont.-in-part of U.S. Provisional Ser. No. 114,718.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6756360	B1	20040629	US 1999-470649	19991222
ZA 2001005016	A	20020919	ZA 2001-5016	20010619
US 2004167178	A1	20040826	US 2004-780948	20040217
PRIORITY APPLN. INFO.:			US 1998-114718P	P 19981224
			US 1999-470649	A3 19991222

OTHER SOURCE(S): MARPAT 141:71536
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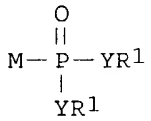

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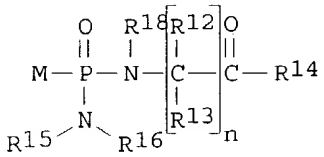

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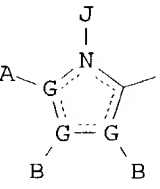

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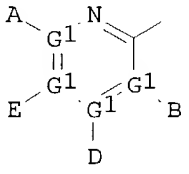


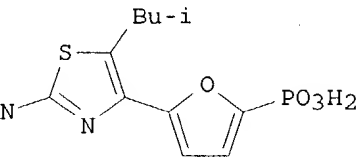
IV

AB Pharmaceutical compns. containing an FBPase inhibitor [I and II; wherein in vivo or in vitro compds. I and II are converted to MPO3-2 which inhibits FBPase; and wherein Y = O, NR6; when Y = O, then R1 = H, alkyl, aryl, etc.; when Y = NR6, then R1 = H, (cycloalkylene)CO2R3, C(R4)2CO2R3, etc.; R3 = alkyl, aryl, aralkyl, alicyclic; R4 = H, alkyl; or together R4 and R4 form a cyclic group; R6 = H, alkyl, acyloxyalkyl, etc.; n = 1-3; R18 = H, alkyl, aryl, etc.; R12, R13 = H, alkyl, aryl, etc.; R14 = OR17, N(R17)2, SR17, etc.; R15 = H, alkyl, aryl, etc.; R16 = alkyl, aryl, aralkyl, etc.; R17 = alkyl, aryl, aralkyl, etc.; M = XR5 (wherein R5 = III and IV; G = C, N, O, S, Se; G1 = C, N; A = H, halo, alkyl, etc.; B, D = H, alkyl, aryl, etc.; E = H, alkyl, alkenyl, etc.; J = H, null; X = alkyl(hydroxy), heteroaryl, alkoxycarbonylamino, etc.); with the provisos] and an insulin sensitizer are provided as well as methods for treating diabetes and diseases responding to increased glycemic control, an improvement in insulin sensitivity, a reduction in insulin levels, or an enhancement of insulin secretion. Syntheses of compds. I are described in 49 synthetic examples. E.g., a multi-step synthesis of 2-amino-5-(2-furanyl)-4-[2-(5-phosphono)furanyl]thiazole, was given.

FERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CESSION NUMBER: 2002:921901 CAPLUS
CUMENT NUMBER: 138:4695
TLE: Preparation of heteroaromatic phosphonates as fructose 1,6-bisphosphatase inhibitors
VENTOR(S): Dang, Qun; Kasibhatla, Srinivas Rao; Reddy, K. Raja; Erion, Mark D.; Reddy, M. Rami; Agarwal, Atul
TENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
URCE: U.S., 129 pp., Cont.-in-part of U.S. Provisional Ser. No. 135,504.
CODEN: USXXAM
CUMENT TYPE: Patent
NGUAGE: English
MILY ACC. NUM. COUNT: 2
TENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6489476	B1	20021203	US 1999-389698		19990903
PT 1112275	T	20031231	PT 1999-954595		19990903
ES 2204170	T3	20040416	ES 1999-954595		19990903
ZA 2001001711	A	20020528	ZA 2001-1711		20010228
US 2004058892	A1	20040325	US 2003-636474		20030806
IORITY APPLN. INFO.:			US 1998-135504P	P	19980909
			US 1998-111077P	P	19981207
			US 1999-389698	A1	19990903
			US 2002-231953	B1	20020830



II

The title compds. R5XP(O)(YR1)2 [I; wherein X = (un)substituted (cyclic) linking group between R5 and P via 1-4 atoms, including 0-1 N, O, or S atoms; or X = urea or carbamate; Y = independently O or NR6; when Y = O, R1 = H, alkyl, (un)substituted (alkyl)aryl or alicyclic, C(R2)2OC(O)NR22, NR2C(O)R3, C(R2)2OC(O)R3, etc.; when Y = NR6, R1 = H, [C(R2)2]qC(O)OR3, C(R4)2C(O)OR3, [C(R2)2]qC(O)SR3, cycloalkylene-C(O)OR3, etc.; R2 = H or R3; R3 = (ar)alkyl, aryl, or alicyclic; R4 = H, alkyl, etc.; R5 = (un)substituted benzothiazolyl, benzoxazolyl, thiazolyl, (is)oxazolyl, imidazolyl, pyrazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, etc.; R6 = H, (acyloxy)alkyl, alkoxycarbonyloxyalkyl, or acyl; q = 1-2], and their prodrugs, were prepared via high throughput and standard synthetic methods. Compds. I and their prodrugs were tested for a variety of biol. activities including inhibition of fructose 1,6-bisphosphatase (FBPase) and activity toward AMP binding enzymes, such as adenosine kinase. Compds. of the invention are useful in the treatment of diabetes and other diseases where inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen storage, or reduction in insulin levels is beneficial. Thus, the phosphonofuranylthiazole (II) was prepared and tested for inhibition of human liver FBTase (IC50 = 0.025 μM), inhibition of gluconeogenesis (IC50 = 2.5 μM), and blood glucose lowering (65% i.v.).
FERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CESSION NUMBER: 2002:51257 CAPLUS
CUMENT NUMBER: 136:123595

TLE: A combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for the treatment of diabetes

VENTOR(S): Van Poelje, Paul D.; Erion, Mark D.; Fujiwara, Toshihiko

TENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA; Sankyo Company, Ltd.

URCE: PCT Int. Appl., 392 pp.
CODEN: PIXXD2

CUMENT TYPE: Patent

NGUAGE: English

MILY ACC. NUM. COUNT: 1

TENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003978	A2	20020117	WO 2001-US21557	20010705
WO 2002003978	A3	20031016		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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US 2003073728	A1	20030417	US 2001-900364	20010705
BR 2001012212	A	20031230	BR 2001-12212	20010705
EP 1372660	A2	20040102	EP 2001-952530	20010705
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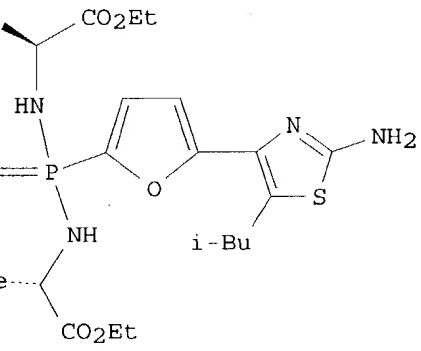
JP 2004508297	T2	20040318	JP 2002-508433	20010705
NO 2003000034	A	20030305	NO 2003-34	20030103

IORITY APPLN. INFO.:

US 2000-216531P	P	20000706
US 2001-900364	A	20010705
US 2000-215126P	P	20000629
WO 2001-US21557	W	20010705

HER SOURCE(S): MARPAT 136:123595



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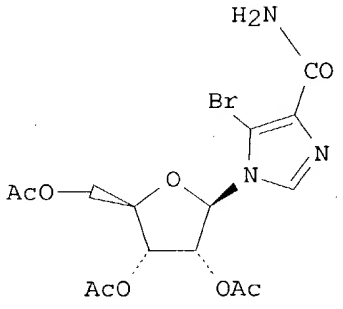

II

A combination therapy of at least one FBPase inhibitor ((R1Y)2P(O)M and R14C(O)(CR12R13)nN(R18)P(O)(NR15R16)M; e.g. 2-amino-5-propylthio-4-(5-phosphono-2-furanyl)thiazole monohydrobromide and 2-amino-5-isobutyl-4-[2-[N,N'-bis[(S)-1-(ethoxycarbonyl)ethyl]phosphonodiamido]-5-furanyl]thiazole (shown as I)) and at least one other antidiabetic agent (insulin secretagogue; e.g. glyburide, a sulfonylurea) is disclosed. (R1Y)2P(O)M and R14C(O)(CR12R13)nN(R18)P(O)(NR15R16)M are converted in vivo or in vitro to MP032-, which inhibit FBPase; the substituents are defined in the claims. General methods and about 15 specific example prepns. of the phosphorus compds. are included but no methods of preparation are claimed. In

the biol. examples, data is presented for the following for selected phosphorus compds. and other materials: inhibition of human liver FBPase, inhibition of rat liver and mouse liver FBPase, inhibition of gluconeogenesis by an FBPase inhibitor in rat hepatocytes, inhibition of glucose production and elevation of fructose-1,6-bisphosphate levels in rat hepatocytes treated with FBPase inhibitors, anal. of hepatic and plasma drug metabolite levels, blood glucose, and hepatic fructose 1,6-bisphosphate levels after administration of compound A (shown as II) p.o. to normal fasted rats, anal. of hepatic and plasma drug levels after administration of compds. i.p. to normal fasted rats, oral bioavailability determination of two compds. and oral glucose lowering activity of two compds. For insulin secretagogues: insulin release from pancreatic islets, glucose lowering in the fasted rat, i.v. glucose tolerance in the fasted rat, oral glucose tolerance in the Zucker diabetic fatty rat, insulin secretion in the rat, inhibition of KATP-channels in mouse pancreatic beta-cells, and sulfonylurea receptor binding. Also included are: inhibition of dipeptidyl peptidase IV (DPP-IV inhibitors), alpha-glucosidase assay, glycogen phosphorylase assay, assay of glucose 6-phosphatase inhibitors, glucagon antagonist assay, amylin agonist assay, fatty acid oxidation inhibitor assay, glucose lowering in the db/db mouse (FBPase inhibitor), glucose lowering in the ZDF rat, acute combination treatment of an insulin secretagogue and an FBPase inhibitor in the ZDF rat, chronic combination treatment of an insulin secretagogue and an FBPase inhibitor in the ZDF rat, acute combination treatment of insulin and an FBPase inhibitor in db/db mice, beneficial effect of chronic combination treatment of insulin and an FBPase inhibitor in db/db mice, and beneficial effect of chronic combination treatment of insulin and an FBPase inhibitor in db/db Mice. Also included are: acute combination treatment of insulin and an FBPase inhibitor in the Goto-Kakizaki rat, acute combination treatment of a biguanide and an FBPase inhibitor in db/db mice, acute combination treatment of an alpha glucosidase inhibitor and an FBPase inhibitor in Goto-Kakizaki rats, acute combination treatment of a glycogen phosphorylase inhibitor and an FBPase inhibitor in db/db or ob/ob mice, acute combination treatment of a glucose-6-phosphatase inhibitor and an FBPase inhibitor in db/db or ob/ob mice, acute combination treatment of an FBPase inhibitor and an amylin agonist, chronic combination treatment of a fatty acid oxidation inhibitor and an FBPase inhibitor in the streptozotocin-induced diabetic rat.

ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER: 2001:489407 CAPLUS
CUMENT NUMBER: 135:76989
TLE: Novel bisamidate phosphonate prodrugs of FBPase inhibitors for use as antidiabetics
VENTOR(S): Jaing, Tao; Kasibhatla, Srinivas Rao; Reddy, Raja K.
TENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
URCE: PCT Int. Appl., 250 pp.
CODEN: PIXXD2
CUMENT TYPE: Patent
NGUAGE: English
MILY ACC. NUM. COUNT: 1
TENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047935	A2	20010705	WO 2000-IB2071	20001222
WO 2001047935	A3	20020321		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2396713	AA	20010705	CA 2000-2396713	20001222
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US 2002173490	A1	20021121	US 2000-747182		20001222
JP 2003519154	T2	20030617	JP 2001-549405		20001222
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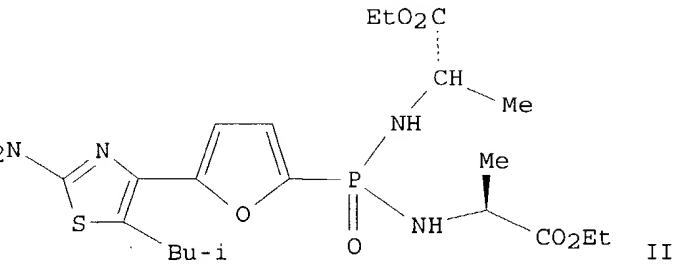
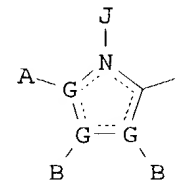
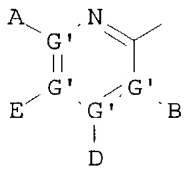
THER SOURCE(S): MARPAT 135:76989







Novel bisamidate phosphonate prodrugs (I; R5XP(O)(NR15R16)NR18(CR12R13)nC(O)R14; e.g. 2-amino-5-isobutyl-4-[5-[N,N'-bis((S)-1-(ethoxycarbonyl)ethyl)phosphonodiamido]-2-furanyl]thiazole (II)) of fructose-1,6-bisphosphatase (FBPase) inhibitors and their use in the treatment of diabetes and other conditions associated with elevated blood glucose were reported. In I, n = 1-3; R2 = R3, H; R3 = alkyl, aryl, alicyclic, and aralkyl; each R12 and R13 = H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R12 and R13 together are connected via 2-6 atoms, optionally including 1-2 heteroatoms = O, N and S, to form a cyclic group; each R14 = OR17, N(R17)2, NHR17, NR20R19 and SR17; R15 = H, lower alkyl, lower aryl, lower aralkyl, or together with R16 is connected via 2-6 atoms, optionally including 1 heteroatom = O, N, and S; R16 = (CR12R13)nC(O)R14, H, lower alkyl, lower aryl, lower aralkyl, or together with R15 is connected via 2-6 atoms, optionally including 1 heteroatom = O, N, and S; each R17 = lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or together R17 and R17 on N is connected via 2-6 atoms, optionally including 1 heteroatom = O, N, and S; R18 = H, lower alkyl, aryl, aralkyl, or together with R12 is connected via 1-4 C atoms to form a cyclic group; each R19 = H, lower alkyl, lower aryl, lower alicyclic, lower aralkyl, and COR3. R5 = III and IV, wherein each G = C, N, O, S, and Se, and wherein only one G may be O, S, or Se, and at most one G is N; each G' = C and N and wherein no more than two G' groups are N; A = H, NR42, CONR42, CO2R3, halo, S(O)R3, SO2R3, alkyl, alkenyl, alkynyl, perhaloalkyl, haloalkyl, aryl, CH2OH, CH2NR42, CH2CN, CN, C(S)NH2, OR2, SR2, NHC(S)NR42, NHAc, null; each B and D = H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, C(O)R11, C(O)SR3, SO2R11, S(O)R3, CN, NR92, OR3, SR3, perhaloalkyl, halo, NO2, and null, all except H, CN, perhaloalkyl, NO2, and halo are optionally substituted; E = H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, C(O)OR3, CONR42, CN, NR92, NO2, OR3, SR3, perhaloalkyl, halo, and null, all except H, CN, perhaloalkyl, and halo are optionally substituted; J = H, null. X is an optionally substituted linking group that links R5 to the P atom via 2-4

atoms, including 0-1 heteroatoms (N, O, and S), except that if X is urea or carbamate there are 2 heteroatoms, measured by the shortest path between R5 and the P atom, and wherein the atom attached to the P is a C atom, and wherein X = -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with COOR2, SO3H, or PO3R22; R2 = R3 and H; R3 = alkyl, aryl, alicyclic, and aralkyl; each R4 = H, and alkyl, or together R4 and R4 form a cyclic alkyl group; each R9 = H, alkyl, aryl, aralkyl, and alicyclic, or together R9 and R9 form a cyclic alkyl group; R11 = alkyl, aryl, NR22, and OR2; and with the proviso that: (1) when G' is N, then the resp. A, B, D, or E is null; (2) at least one of A and B, or A, B, D, and E is not selected from the group consisting of H or null; (3) when G is N, then the resp. A or B is not halogen or a group directly bonded to G via a heteroatom. Approx. 700 antidiabetic title compds. were prepared by standard methods. Results are reported of tests of some of the prodrugs and/or the related phosphonic acids for inhibition of human liver FBPase, inhibition of rat liver FBPase, inhibition of gluconeogenesis in rat hepatocytes, chemical stability, oral bioavailability in rats, oral pharmacokinetics in rats, acute and chronic oral efficacy in the ZDF rat, and structure activity relationship of human liver phosphoramidase. E.g., 2-amino-5-isobutyl-4-[5-phosphono-2-furyl]thiazole, resulting from the hydrolysis of the prodrug, exhibited an IC50 of 0.025 μM against human liver FBPase and an IC50 of 2.5 μM as inhibitor of glucose production in rat hepatocytes.

3 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 2000:456867 CAPLUS
OCUMENT NUMBER: 133:84284
ITLE: A combination of fructose-1,6-bisphosphatase (FBPase) inhibitors and insulin sensitizers for the treatment of diabetes
NVENTOR(S): Erion, Mark D.; Vanpoelje, Paul
ATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
OURCE: PCT Int. Appl., 306 pp.
CODEN: PIXXD2
OCUMENT TYPE: Patent
ANGUAGE: English
AMILY ACC. NUM. COUNT: 2
ATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038666	A2	20000706	WO 1999-US30713	19991222
WO 2000038666	A3	20011129		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2354053	AA	20000706	CA 1999-2354053	19991222
EP 1143955	A2	20011017	EP 1999-964313	19991222
EP 1143955	A3	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9917005	A	20020402	BR 1999-17005	19991222
JP 2003515523	T2	20030507	JP 2000-590620	19991222
AU 771039	B2	20040311	AU 2000-20583	19991222
RU 2227749	C2	20040427	RU 2001-120726	19991222
ZA 2001005016	A	20020919	ZA 2001-5016	20010619
NO 2001003115	A	20010824	NO 2001-3115	20010621
RIORITY APPLN. INFO.:			US 1998-114718P P	19981224

WO 1999-US30713 W 19991222

ER SOURCE(S): MARPAT 133:84284

Pharmaceutical compns. containing an FBPase inhibitor and an insulin sensitizer are provided as well as methods for treating diabetes and diseases responding to increased glycemic control, an improvement in insulin sensitivity, a reduction in insulin levels, or an enhancement of insulin secretion.

ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ESSION NUMBER: 2000:175817 CAPLUS

UMENT NUMBER: 132:222529

LE: Preparation of heteroaromatic phosphonates as fructose 1,6-bisphosphatase inhibitors

ENTOR(S): Dang, Qun; Kasibhatla, Srinivas Rao; Reddy, K. Raja; Erion, Mark D.; Reddy, M. Rami; Agarwal, Atul

ENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA

RCE: PCT Int. Appl., 338 pp.
CODEN: PIXXD2

UMENT TYPE: Patent

GUAGE: English

ILY ACC. NUM. COUNT: 2

ENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000014095	A1	20000316	WO 1999-US20346		19990903
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2343027	AA	20000316	CA 1999-2343027		19990903
EP 1112275	A1	20010704	EP 1999-954595		19990903
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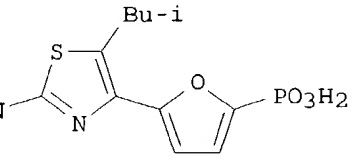
BR 9913532	A	20011002	BR 1999-13532		19990903
JP 2002524463	T2	20020806	JP 2000-568853		19990903
AU 761267	B2	20030529	AU 2000-10905		19990903
NZ 510308	A	20030630	NZ 1999-510308		19990903
AT 246197	E	20030815	AT 1999-954595		19990903
PT 1112275	T	20031231	PT 1999-954595		19990903
ES 2204170	T3	20040416	ES 1999-954595		19990903
ZA 2001001711	A	20020528	ZA 2001-1711		20010228
NO 2001001174	A	20010509	NO 2001-1174		20010307
ORITY APPLN. INFO.:			US 1998-135504P	P	19980909
			US 1998-111077P	P	19981207
			WO 1999-US20346	W	19990903

IER SOURCE(S): MARPAT 132:222529



II

The title compds. R5XP(O)(YR1)2 [I; wherein X = (un)substituted (cyclic) linking group between R5 and P via 1-4 atoms, including 0-1 N, O, or S atoms; or X = urea or carbamate; Y = independently O or NR6; when Y = O,

R1 = H, alkyl, (un)substituted (alkyl)aryl or alicyclic, C(R2)2OC(O)NR22, NR2C(O)R3, C(R2)2OC(O)R3, etc.; when Y = NR6, R1 = H, [C(R2)2]qC(O)OR3, C(R4)2C(O)OR3, [C(R2)2]qC(O)SR3, cycloalkylene-C(O)OR3, etc.; R2 = H or R3; R3 = (ar)alkyl, aryl, or alicyclic; R4 = H, alkyl, etc.; R5 = (un)substituted benzothiazolyl, benzoxazolyl, thiazolyl, (is)oxazolyl, imidazolyl, pyrazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, etc.; R6 = H, (acyloxy)alkyl, alkoxycarbonyloxyalkyl, or acyl; q = 1-2], and their prodrugs, were prepared via high throughput and standard synthetic methods. I and their prodrugs were tested for a variety of biol. activities including inhibition of fructose 1,6-bisphosphatase (FBPase) and activity toward AMP binding enzymes, such as adenosine kinase. Compds. of the invention are useful in the treatment of diabetes and other diseases where inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen storage, or reduction in insulin levels is beneficial. Thus, the phosphonofuranylthiazole (II) was prepared and tested for inhibition of human liver FBTase (IC50 = 0.025 μM), inhibition of gluconeogenesis (IC50 = 2.5 μM), and blood glucose lowering (65% i.v.).